Heparin Therapy in Autoimmune Hemolytic Anemia

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At present, corticosteroids and splenectomy constitute the main forms of therapy in autoimmune hemolytic anemia. In general, the patient is given a large dose of prednisone for a short period until the hemolytic process abates, then the dose of corticosteroid is reduced to the minimum dose which controls the disease. If this maintenance dose for the individual patient is too high to permit prolonged administration without producing undesirable side effects of hypercorticism, splenectomy must be considered. Opinions appear to differ, however, on the length of time one is justified in delaying splenectomy when response to corticosteroids is suboptimal.

One reason for reluctance to undertake splenectomy early in management of a case is the relatively high relapse rate following the procedure. This has been recognized for a number of years and is as high as 50 per cent in some series. When relapse does occur following splenectomy, corticosteroids may be helpful, but occasionally one is confronted with a patient in whom it is impossible to produce a remission with either splenectomy or corticosteroids. In such cases, courses of nitrogen mustard have been administered in an effort to ameliorate the disease by depressing antibody formation. Results have been generally unsatisfactory. In 1956, Tocantins and Wang reported the use of radioactive gold intravenously in seven patients who had relapsed following splenectomy. Six of the seven had partial or complete control of the hemolytic process for variable periods following the injections.

Owren was first to attempt to treat autoimmune hemolytic anemia with heparin. A 74 year old man, with severe hemolytic anemia, was given 350 mg. of heparin daily for nine days and later 800 mg. daily for six days. The smaller dose had little effect on the rate of hemolysis, whereas the larger dose appeared to control the disease quite effectively. Unfortunately, heparin had to be discontinued because of a bleeding tendency so the results were inconclusive. Noteworthy, however, was the rapid return of severe hemolysis upon cessation of heparin.

In 1956, Storti, Vaccari and Baldini reported a clinical trial of heparin in autoimmune hemolytic anemia with good evidence of beneficial results from 250 mg. daily over a period of 30 days. When the patient became asymptomatic, he discontinued heparin without consultation and "...again showed a violent onset of the hemolytic process."

Roth and Frumin in 1956 demonstrated decreases in direct and indirect
Coombs titers, plasma hemoglobin and serum bilirubin within hours following single injections of 50 mg. heparin in autoimmune hemolytic anemia. However, heparin was not administered to this patient regularly as a therapeutic procedure.

To our knowledge, these cases constitute the only recorded instances of heparin therapy in autoimmune hemolytic disease. Therefore, we report the strikingly beneficial effects of heparin in an unusually severe case of autoimmune hemolytic anemia, unresponsive to corticosteroids and splenectomy.

**Case History**

R. T. was a 19 year old Negro Marine who was aboard ship in the Mediterranean area in June, 1958, when he noted the onset of progressive fatigue and exertional dyspnea. Two weeks later, additional symptoms of dizziness, headaches, roaring in the ears and extreme weakness of the legs were noted. On the morning of June 25, 1958, he suffered a syncopal attack and was found to have a hemoglobin of 6.0 Gm./100 ml. The patient was immediately evacuated to an Air Force Hospital, where a hemoglobin of 4.0 Gm. was recorded with 60 per cent reticulocytes. Sickled cell preparations were negative. Six units of blood were administered, and he was transferred to another Air Force Hospital.

The patient appeared acutely ill and moderately icteric, with temperature of 105 F., pulse 126 and respirations 48 per minute. A loud, harsh pericardial friction rub was heard. The liver was felt 6 cm. below the right costal margin, but the spleen was not palpable. Working diagnoses were hemolytic anemia with pericarditis and myocarditis. Therapy with prednisone, 80 mg. per day, was instituted, plus antibiotics and digitalis. There was temporary improvement, but four days later petechiae developed on the chest, and the hemoglobin, which had remained around 9.0 Gm., fell to 4.1 Gm., the WBC count was 20,000/cu.mm. and platelets 75,000. Bone marrow films were interpreted as consistent with hemolytic anemia. Direct and indirect Coombs tests were positive; repeated L.E. tests were negative. It was impossible to type and cross match the patient's blood due to autoagglutination, so he was given 3 units of O-negative blood.

On July 9, 1958 an exchange transfusion was undertaken with 20 U. of O-negative blood; the post-transfusion hemoglobin level was 14.1 Gm. The next day hematemesis and melena developed suddenly; bilirubin rose to 20 mg. per cent and the patient appeared terminal. However, with more transfusions his hemoglobin was temporarily stabilized around 7.0 Gm. and he was transferred to the Air Force Hospital, Weisbaden, Germany, for consideration of splenectomy.

Repeat laboratory studies at this facility showed hemoglobin 7.2 Gm., platelets 58,000 (direct count), reticulocytes 7.8 per cent, positive direct and indirect Coombs tests. Prednisone administration was discontinued and ACTH, 200 U. daily, was given without apparent effect on the hemolytic process. On July 27, 1958 splenectomy was performed. The spleen was described as approximately twice the normal size; two small accessory spleens were excised. Microscopic sections of the spleen were consistent with hemolytic anemia. Five days after the operation, the hemoglobin fell to 5.8 Gm.; serum bilirubin was 3.6 mg. per cent. Transfusions were again administered, and the patient was transferred to the U. S. Naval Hospital, Bethesda, Md., on August 8, 1958, having received more blood en route.

He appeared acutely ill with marked scleral icterus and moderate pallor of mucous membranes. Heart and lungs were essentially normal. The liver was palpable 6 cm. below the right costal margin. There was a healing splenectomy scar in the left upper quadrant and a 2 cm. old scar in the left supraclavicular area. Direct questioning regarding the latter scar revealed that a "lump" had been removed 1 to 2 years prior to his entry into the service. Subsequent attempts to get further information about that episode were unsuccessful.

The hemoglobin was 10.0 Gm., hematocrit 30 per cent, platelets 290,000, reticulocytes 2.8 per cent, WBC 11,500, leucocytic differential showed 2 bands, 43 segmented neutro-
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phils, 38 lymphocytes, 17 monocytes, and 8 nucleated red cells per 100 WBC. Examination of the stained blood film revealed spherocytes, occasional immature white cells and moderate polychromasia. Aspirated bone marrow showed marked erythroid hyperplasia, increased iron content and evidence of erythrophagocytosis. Total bilirubin was 11.2 mg. per cent with 4.2 direct and 7.0 indirect. Direct and indirect Coombs tests were positive. Serologic tests for syphilis were negative. Hemoglobin electrophoresis showed hemoglobin A. Serum electrophoresis revealed 22 per cent gamma globulin (normal 12 to 16 per cent) with essentially normal distribution of the remaining fractions. Antibody studies failed to reveal specificity for a blood group.

Administration of ACTH was discontinued and prednisone, 160 mg. day, was given instead. At least 1 unit of blood was required daily to maintain the hemoglobin above 5.0 Gm. On August 15, 1958, heparin therapy was started as a single daily 150 mg. dose injected into adipose tissue (Lipo-Hepin, Darwin). Within one week, the hemoglobin stabilized between 8 to 9 Gm. and total bilirubin dropped to 1.6 mg. per cent and stabilized. Direct and indirect Coombs tests were negative when tested two weeks later.

In an effort to determine the role of heparin in producing this remission, the dosage of prednisone was reduced to 40 mg. daily and on September 6, 1958 heparin was discontinued after reducing the dose over a 4 day period. On the morning of September 14, 1958, the patient complained of precordial pain. Scleral icterus was obvious and a loud pericardial friction rub was heard. Hemoglobin was 6.0 Gm. per cent, WBC 24,600, platelets 350,000, bilirubin, 1.7 mg. per cent; direct and indirect Coombs tests were negative. The hemoglobin appeared to remain stable after transfusions so prednisone, 40 mg. daily, was continued in an effort to ascertain its single effectiveness in controlling the hemolytic process. It was soon obvious that his hemoglobin was again gradually dropping, and so on October 10, 1958 heparin injections, 150 mg./day, were re instituted. Again, the hemolytic process was controlled; this time prednisone was again reduced and finally discontinued.

The patient's improvement was striking; during November and December, 1958, he was up and about doing ward duties and was completely asymptomatic. In December, the dose of heparin was gradually reduced and the patient was sent home for Christmas vacation, having been taught to administer 20 mg. of heparin to himself daily.

On return to the hospital, he continued to be free of symptoms. Hemoglobin was 10.6 Gm. and bilirubin was 0.8 mg. per cent. In view of an apparent remission and in order further to establish its effectiveness, heparin was discontinued. The patient's condition remained stable until January 17, 1959, when he suddenly developed generalized petechiae. The platelet count was 12,000 and repeat bone marrow aspiration showed numerous megakaryocytes with only slight erythroid hyperplasia. Platelet antibodies were not demonstrable. Prednisone was given without much effect on the platelet count, and within a few days it was obvious that the hemolytic process was extremely active again with positive direct Coombs test. In spite of prednisone, the platelet count fell to 1500, and it was felt that heroic measures were justified. Heparin, 50 mg. daily, was restarted in the hope that it might influence the hemolysis and thrombocytopenia favorably. Surprisingly, the platelet count rose to 85,000 for a short time, but epistaxis, which had been minor and intermittent before heparin therapy, became massive on February 16, 1959, and heparin was stopped. The hemorrhage was readily controlled, but severe hemolysis and thrombocytopenia continued in spite of large doses of prednisone and ACTH. The patient's condition gradually deteriorated, the bilirubin reaching 78 mg. per cent with direct 51 and indirect 27 over a period of several days. He lapsed into coma and expired on March 4, 1959.

Pertinent Autopsy Findings

The skin and mucous membranes were deeply jaundiced. Pleural and pericardial spaces were obliterated by diffuse fibrinous adhesions. The liver weighed 3200 Gm. and displayed marked biliary stasis without calculi. A 3 cm. accessory spleen was found near the cardia of the stomach. Several retroperitoneal lymph nodes were enlarged and matted together to form a mass which protruded from the preaortic area. Microscopic examination of the nodes showed cellular areas containing typical Reed-Sternberg cells and necrotic
Fig. 1.—The beneficial effect of heparin in severe autoimmune hemolytic anemia secondary to Hodgkin's disease in a 19 year old Negro male. The terminal thrombocytopenia is also demonstrated.
areas containing aspergilli. Pleura and epicardium showed only inflammatory cells microscopically. The final diagnosis was retroperitoneal Hodgkin's disease.

**DISCUSSION**

Although the effects of heparin in hemolytic systems have been studied by a number of investigators using in vitro and in vivo experiments, its mode of action remains an enigma. Storti and Vaccari demonstrated that some anticoagulants prevent hemolysis in vitro and concluded that this was due to their anticomplementary activity. In a later report by these authors, the same conclusion was reached following in vivo experiments in animals and man. Roth and Frumin came to a similar conclusion after demonstrating that injections of heparin produced a prompt decrease in direct and indirect Coombs titers, plasma hemoglobin and serum bilirubin in a patient with acquired hemolytic anemia. They felt that the beneficial effect might be due to a competition for complement.

Gold and Fotino demonstrated a decrease in complement in experimental and acquired hemolytic anemias, and simultaneously in these sera found an increase in anticomplementary activity. Similar results were observed by Van Loghem et al., who studied warm and cold agglutinins and hemolysins in 168 sera from patients with various diagnoses, including acquired hemolytic anemia and disseminated lupus erythematosus. In general, low levels of complement were found in hemolytic anemias in which warm antibodies and/or hemolysins could be demonstrated. Jordan reported low levels of complement in three cases of acquired hemolytic anemia, but, on the other hand, he found normal levels in three others. Similar variations were noted by Dacie, who concluded that complement has very little to do with hemolysis in vivo.

In our patient, the titer of complement was determined at a time when he was receiving frequent transfusions; the value was slightly higher than normal. In an effort to detect anticomplementary activity, Wasserman tests were conducted with the patient’s serum during the periods of heparin administration. These failed to demonstrate anticomplementary activity, although admittedly, this may be a very crude measure.

In more recent experiments, some of which were stimulated by the results in our patient, Roth has demonstrated that serum concentrations of heparin, following therapeutic doses, are minute and rarely demonstrate anticomplementary activity by any test. He concludes, as a result of these observations, that the beneficial effects of heparin in acquired hemolytic anemia are not due to its anticomplementary effect.

Whatever the theories may be regarding the mode of action of heparin in autoimmune hemolytic anemia, the results in our patient seem to corroborate its beneficial effects. This is even more striking when one considers the extreme hemolytic activity in this patient, its refractoriness to conventional forms of therapy, and the fact that it was controlled for weeks by as little as 20 mg. of heparin given once daily. Obviously, such results are subject to the usual criticisms of any clinical and therapeutic observation, specifically, the natural variations in the rate of hemolysis from one period to the next,
the activity of the basic disease process and the effect of all other therapeutic measures. In an effort to resolve these points we attempted to vary the courses of heparin as much as seemed feasible in relation to corticosteroids and the course of the disease. The results suggest that the periods of remission were due to heparin and not to any beneficial or even synergistic effect of the corticosteroids.

We were particularly impressed, as others have been, by the sudden return of severe hemolysis after a lag period following cessation of heparin therapy. On the basis of this experience, we feel that continuous heparin administration is indicated in an effort to delay fatal hemolytic crisis in severe cases. Such administration is entirely feasible and practical; the patient may be taught to give the heparin to himself.

The beneficial effect of transfusions during heparin administration was striking. Without heparin, it appeared that donor cells were immediately scheduled for destruction, and any rise in hemoglobin was very fleeting; whereas, during heparin administration, a unit of blood produced a greater and a more sustained rise in hemoglobin. The direct and indirect Coombs tests became negative during heparin administration, suggesting that heparin interfered in some way with the coating of red cells with globulin.

The final phase of our patient’s illness resulted from the not uncommon combination of hemolytic anemia and thrombocytopenia; both processes were extreme. At that time, severe nosebleeds contributed to the blood loss, and heparin therapy seemed completely illogical and open to criticism. Nevertheless, results with large doses of prednisone were so dismal that unorthodox measures seemed justified. Also, as reasoned by Evans et al., the thrombocytopenia accompanying cases of autoimmune hemolytic anemia is probably the result of an antibody-like mechanism similar to the one causing hemolysis. Heparin therapy was associated, fortuitously or not, with a rather prompt rise in platelets. Unfortunately, the rise was only temporary, and epistaxis continued to be such a serious problem that heparin was stopped.

Finally, the autopsy finding of Hodgkin’s disease involving retroperitoneal nodes came as a mild surprise since we had almost forgotten our unsuccessful attempts to obtain information about a supraclavicular lymph node biopsy done three years earlier. Throughout the illness the hemolytic anemia, recurrent pericarditis, pleuritis, joint pains and effusions led us toward a working diagnosis of disseminated lupus erythematosus, in spite of repeatedly negative L.E. tests.

**Summary and Conclusions**

1. Although a few previous reports suggest a beneficial effect of heparin in autoimmune hemolytic anemia, there has been no general recognition of this form of treatment. Therefore, its striking benefit in a patient with severe autoimmune hemolytic anemia refractory to usual therapeutic measures has been reported.

2. The mechanism of action of heparin in autoimmune hemolytic anemia remains unknown; it does not appear to be due to any anticomplementary activity.
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3. Heparin should be tried more widely in autoimmune hemolytic anemia, particularly in situations in which response to corticosteroids and splenectomy has been disappointing.

SUMMARIO IN INTERLINGUA

1. Ben que varie previe reportos pareva demonstrar que il resulta un effecto benefic del uso de heparina in le tractamento de anemia hemolytic autoimmun, iste forma de therapia non es generalmente recognoscite. A causa de isto, le presente reporte es presentate, concernente le frappante beneficios obtenite ab ille therapia per un paciente con anemia hemolytic autoimmun que esseva refractori a omne le usual mesuras therapeutic.

2. Le mechanismo del action de heparina in anemia hemolytic autoimmun remane obscur. Illo non pare esser un question de activitate anticomplementari.

3. Heparina debereva esser essayate plus extensemente in le tractamento de anemia hemolytic autoimmun, specialmente in situationes in que le responsa al uso de corticosteroides e al effectuation de splenectomia es disappunctante.

REFERENCES


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